UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,241	01/17/2002	Bernhard Hauer	50531	6324

26474 7590 11/29/2007

NOVAK DRUCE DELUCA & QUIGG, LLP
1300 EYE STREET NW
SUITE 1000 WEST TOWER
WASHINGTON, DC 20005

EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
11/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/031,241	HAUER ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex.parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1-10,13-15 and 19-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-12 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☑ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☑ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-22 are pending. Claims 1-10, 13-15 and 19-22 are withdrawn. Claims 11-12 and 16-18 are under consideration.

Response to Arguments

In view of the appeal brief filed on August 22, 2007 PROSECUTION IS HEREBY REOPENED. New grounds of objection are set forth below.

In view of the appeal brief filed on August 22, 2007, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

Response to Arguments

Applicant's amendment and arguments filed on August 22, 2007, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied.

Claim Rejections - 35 USC § 112-2nd paragraph

In view of applicants argument, the rejection of claim 12 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been **withdrawn**.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-12 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 11-12 and 16-18 are drawn to a method for the enzymatic production of terminally or subterminally hydroxylated fatty acids from fatty acids recited in claim 11 by using a cytochrome P450 monooxygenase and electron donor system comprising a non-electrode-bound source of electrons and a mediator.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." In this case, the examiner has broadly the claims to encompass a method of enzymatic production of terminally or subterminally hydroxylated fatty acids using any or all cytochrome P450

monooxygenase, including any recombinants, variants and mutants from any source and/or any or all electron donor system comprising a non-electrode-bound source of electrons. Therefore, the claims are drawn to a method for enzymatic production of terminally or subterminally hydroxylated fatty acids using a genus of cytochrome P450 monooxygenase having any structure and/or any or all electron donor system, comprising a non-electrode-bound source of electrons, having any structure.

In *University of Calfornia v. Eli Lilly & Co.,* 43 USPQZd 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, (or) chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The recitation of "cytochrome P450 monooxygenase" fails to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in UC California v. Eli Lilly, (43 USPQ2d 1398) stated that: "in claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Similarly with the claimed method of using a genus of "cytochrome P450 monooxygenase" proteins, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus.

Therefore, in the instant case, the claim is drawn to a method of enzymatic production of terminally or subterminally hydroxylated fatty acids using any or all cytochrome P450 monooxygenase having any structure and/or any or all electron donor system having any structure. The specification only describes a method of hydroxylating fatty acids described in Examples 2-4 of the specification using specific

cytochrome P450 monooxygenase obtained from *Bacillus megaterium* and zinc/Co(III)sepulchrate electron donor system. While MPEP 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In view of the widely variant species encompassed by the genus, this one example is not enough and does not constitute a representative number of species to describe the whole genus of any or all variants, recombinant and mutants of any or all polypeptides having cytochrome P450 monooxygenase activity isolated from any or all source, including any or all variants, recombinants and mutants thereof, and there is no evidence on the record of the relationship between the structure of the cytochrome P450 monooxygenase isolated from Bacillus megaterium and the structure of any or all recombinant, variant and mutant of any or all polypeptides having cytochrome P450 activity. Therefore, the specification fails to describe a representative species of the genus comprising any or all polypeptides having cytochrome P450 monooxygenase activity, including any or all variants, recombinants and mutants thereof.

Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the instant claims are fully described because (1) the claims are not directed to an unknown gene function or structure, but are directed to a method of using cytochrome P450 monooxygenase, (2) oxidation of reactions using P450 enzymes are well known in the art and (3) cytochrome P450 monooxygenases are well known in the art. Examiner respectfully disagrees. While it is true that the instant invention is drawn to a method claim, the claims still involve a genus comprising any or all cytochrome P450 monooxygenase. In *University of Calfornia v. Eli Lilly & Co.,* 43 USPQZd 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, (or) chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient

to show that Applicant was in possession of the claimed genus. In addition, MPEP 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In the instant case, the claims are drawn to a method involving a wide genus comprising any or all cytochrome P450 monooxygenase, isolated from any or all source, including any or all mutants, recombinants or variants thereof, and a wide genus comprising any or all electron donor system comprising any or all non-electrode-bound source of electrons.

Further, the recitation of "cytochrome P450 monooxygenase (E.C. 1.14)" fails to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in UC California v. Eli Lilly, (43 USPQ2d 1398) stated that: "in claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Similarly with the claimed genus of "cytochrome P450 monooxygenase (E.C. 1.14)" proteins, the functional definition of the

genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus.

Hence the rejection is maintained.

Claims 11-12 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of hydroxylating fatty acids described in Examples 2-4 of the specification using a cytochrome P450 monooxygenase obtained from *Bacillus megaterium* and zinc/Co(III)sepulchrate, does not reasonably provide enablement for such a method of hydroxylating fatty acids using any or all variants, mutants and recombinants of any or all cytochrome P450 monooxygenase and any or all electron donor system comprising any or all non-electrode-bound source of electrons. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 11-12 and 16-18 are drawn to a method for the enzymatic production of terminally or subterminally hydroxylated fatty acids from fatty acids recited in claim 11 by using a cytochrome P450 monooxygenase and electron donor system comprising a non-electrode-bound source of electrons and a mediator.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." In this case, the examiner has broadly the claims to encompass a method of enzymatic production of terminally or subterminally hydroxylated fatty acids using any or all cytochrome P450 monooxygenase, including any recombinants, variants and mutants from any source and/or any or all electron donor system comprising a non-electrode-bound source of electrons. Therefore, the claims are drawn to a method for enzymatic production of terminally or subterminally hydroxylated fatty acids using cytochrome P450 monooxygenase having any structure and/or any or all electron donor system, comprising a non-electrode-bound source of electrons, having any structure.

The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of serine proteases isolated from any or all source, including any or all mutants, recombinants and variants thereof. In the instant case, the specification enables only a method of hydroxylating fatty acids described in Examples 2-4 of the specification using specific cytochrome P450 monooxygenase obtained from *Bacillus megaterium* and zinc/Co(III)sepulchrate electron donor system.

The state of prior art, the relative skill of those in the art, and predictability or unpredictability of the art.

Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. In addition, the art does not provide any teaching or guidance as to (1) which amino acids within a cytochrome P450 monooxygenase can be modified and which ones are conserved such that one of skill in the art can make the recited polypeptides having the same biological activity as that of the cytochrome P450 monooxygenase isolated from *Bacillus megaterium*, (2) which segments of a cytochrome P450 monooxygenase are essential for activity, and (3) the general tolerance of cytochrome P450 monooxygenase to structural modifications and the extent of such tolerance. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused

by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions.

The amount of direction or guidance presented and the existence of working examples.

The specification discloses a method of hydroxylating fatty acids described in Examples 2-4 of the specification using specific cytochrome P450 monooxygenase obtained from *Bacillus megaterium* and zinc/Co(III)sepulchrate electron donor system. However, the speciation fails to provide any information as to (1) specific substrates associated with any cytochrome P450 monooxygenase isolated from any source, including variants, mutants and recombinants thereof, (2) structural elements required in a polypeptide having cytochrome P450 monooxygenase activity, or (3) which are the structural elements in a serine protease that are essential to display cytochrome P450 monooxygenase activity. No correlation between structure and function of having cytochrome P450 monooxygenase activity has been presented. There is no information or guidance as to which amino acid residues in the cytochrome P450 monooxygenase isolated from *Bacillus megaterium* can be modified and which ones are to be conserved to create a polypeptide displaying the same activity as that of the cytochrome P450 monooxygenase isolated from Bacillus megaterium.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification.

While enzyme isolation techniques, recombinant and mutagenesis techniques were known in the art at the time of the invention, e.g. hybridization or mutagenesis, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Furthermore, it is not routine in the art to create variants of polynucleotides encoding polypeptides having the activity recited without any knowledge as to the structural features which would correlate with that activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of using any cytochrome P450 monooxygenase having any structure and an electron donor system of any structure. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any or all mutants, variants and recombinants of any or all polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that in view of the state of the art as well as the examples and significant direction provided in the specification, one of ordinary skill in the art could make and use the claimed invention without undue experimentation since hydroxylation techniques and cytochrome P450 monooxygenases are well known to the skilled artisan. Examiner respectfully disagrees. Even though the structure of some cytochrome P450 monooxygenases are known, as applicants have stated, the invention encompasses using any cytochrome P450 monooxygenase, including any or all mutants, variants and recombinants of any PQQGDH, and any or all non-electrode-bound source of electrons to hydroxylate said fatty acid. As discussed above, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a specific knowledge of and guidance with regard to which specific amino acids in the protein's sequence, can be modified such that the modified polypeptide continues to have said claimed activity. Further, the specification does not provide a universal method to terminally and subterminally hydroxylate fatty acids using any or all cytochrome P450 monooxygenase and any or all electron donor system comprising any or all non-electrode-bound source of electrons and a rational and predictable scheme for selecting any fatty acids, cytochrome P450 monooxygenase and electron donor system with an expectation of terminally or subterminally hydroxylating any fatty acids. It is this specific guidance that applicants do not provide. Without specific guidance, those skilled in the art will be subjected to undue

experimentation of making and testing each of the enormously large number of cytochrome P450 monooxygenases and electron donor system comprising any or all non-electrode-bound source of electrons that results from such experimentation.

Hence the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-12 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Estabrook et al. in view of Creaser et al. and Conrad et al.

Claim 11-12 and 16-18 drawn to a method for the enzymatic production of terminally or subterminally hydroxylated fatty acids comprising hydroxylating fatty acids in the presence of an electro donor system, a cytochrome P450 monooxygenase, and oxygen, wherein said electron donor system is zinc/Co(III)sepulchrate.

Estabrook et al. (*Methods in Enzymology* – form PTO-1449) discloses a method for the enzymatic production of terminally or subterminally hydroxylated fatty acids comprising hydroxylating fatty acids in the presence of an electron donor system, a cytochrome P450 monooxygenase, oxygen, chloride ions and a hydrogen peroxide-cleaving enzyme, wherein said fatty acid is a C-12 fatty acid and wherein said electron

donor system comprises an inorganic, non-electrode-bound source of electrons and a mediator (pages 45-46). The method of Estabrook et al. uses a Co(III)sepulchrate mediator of Creaser et al. because "it retains chirality during reversible oxidation-reduction" (page 45, 1st paragraph).

The difference between the reference of Estabrook et al. and the instant invention is that the reference of Estabrook et al. does not teach a method of producing terminally or subterminally hydroxylated fatty acids using a Zn metal in powder from.

Creaser et al. (J. Am. Chem. Soc – form 1449) discloses a Zn/Co(III)sepulchrate electron donor system, which pioneered for the use of Co(III)sepulchrate as mediators in electrochemical reactions (Faulkner et al. – form PTO-1449, Reipa et al. – US Patent 6,126,795 and Roberts et al. – US Patent 6,492,132), wherein the Co(III)sepulchrate mediator is the same mediator used by Estabrook et al. Creaser et al. teaches that Zn dust causes reduction of the Co(III)sepulchrate mediator within seconds (page 3181).

Conrad et al. (J. Am. Chem. Soc. 1989, 111, 3461-3463 – form PTO-892) discloses use of cobalt-cage complexes, such as the Zn/Co(III)sepulchrate, in electron transfer reactions in biological systems, such as cytochrome proteins (page 3461).

Therefore, in combining the teachings of Estabrook et al., Creaser et al. and Conrad et al., it would have been obvious to one having ordinary skill in the art to use either Zn dust as originally taught by Creaser et al. or Pt as taught by Estabrook et al. in hydroxylating fatty acids using a metal/Co(III)sepulchrate electron donor system. One of ordinary skill in the art would have been motivated to use Zn dust because Creaser et

al. teaches that Zn dust causes immediate reduction and because Zn dust is widely available (Sigma) and Conrad et al. discloses general use of Zn/Co(III)sepulchrate in electron transfer reactions in biological systems. One of ordinary skill in the art would have had a reasonable expectation of success since Estabrook et al. teaches a method of hydroxylating fatty acids with cytochrome P450 monooxygenases by replacing NADPH with an electrochemically generated reduction by the mediator Co(III)sepulchrate and Creaser et al. teaches a method of generating two electrons using the mediator Co(III)sepulchrate and Zn dust as the source of electrons.

Therefore, the above references render claims 11-12 and 16-18 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended.

Applicants argue that the claims are not obvious because there is no suggestion/guidance in Creaser et al. or Estabrook et al. to use Zn dust in a biochemical system. Applicants should note that the rejection has been amended. Newly cited reference Conrad et al. discloses use of cobalt-cage complexes, such as the Zn/Co(III)sepulchrate, in electron transfer reactions in biological systems, such as cytochrome proteins (page 3461).

Applicants also argue that one of ordinary skill in the art would have expected success with a reducing agent which is soluble in the reaction mixture rather than the metal-based system of Creaser et al., as taught by Fang et al. Examiner respectfully

disagrees. One having ordinary skill in the art would not have looked to Fang et al. to improve/modify the method of Estabrook et al. Rather, one having ordinary skill in the art would have looked to Creaser et al. and Conrad et al. in modifying the method of Creaser et al. because Creaser et al. teaches that Zn dust causes reduction of the Co(III)sepulchrate mediator within seconds (page 3181). Therefore, it would have been obvious to one having ordinary skill in the art to use either Zn dust as originally taught by Creaser et al. or Pt in the method taught by Estabrook et al.

Applicants also assert that the claimed invention also produces superior and unexpected results. Examiner respectfully disagrees. The instant rejection is not based on Estabrook et al. alone. The relative rates of the electron donor system for Estabrook et al. and Zn/Co(III)sepulchrate electron donor system is irrelevant because the rejection is based on the combined teachings of Estabrook et al., Creaser et al. and Conrad et al. Further, Examiner notes that the claims do not recite any such limitations on the rate of reaction.

Hence the rejection is maintained.

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Yong D. Pak

Patent Examiner 1652